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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,101	05/26/2006	Brian Smith	68.US2.PCT	2470

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ARENA PHARMACEUTICALS, INC.
6166 NANCY RIDGE DRIVE
SAN DIEGO, CA 92121

EXAMINER	
LEESER, ERICH A	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
09/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,101	SMITH ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3,9,11,12,17,19-37,39,45,46,48,49,51,52,54,59,79 and 80 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,9,11,12,17,19-37,39,45,46,48,49,51,52,54,59,79 and 80 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-80 are currently pending.

Priority

Acknowledgement is made that this application is a 371 of PCT/US04/19540, filed on June 17, 2004, and which claims benefit of provisional application 60/480,045, filed on June 20, 2003.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making solvates of the claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the

breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention:

The invention is drawn to the compounds of Formula (I), "or a pharmaceutically acceptable salt, hydrate or solvate thereof." The specification is not adequately enabled to show how to make solvates of the compounds of Formula (I). The compounds of Formula (I) embrace N-phenyl-piperazine derivatives that are modulators of the $5HT_{2C}$ receptor.

Even a cursory calculation of the number of compounds embraced in the instant Formula (I) would result in at least hundreds of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. For instance, claims 27-29 contain approximately 105 exemplified compounds. Thus, the genus embraced in claim 1 is too large and there is no teaching of any solvate of this large genus.

The state of the prior art:

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley,

New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

The predictability or lack thereof in the art:

For the reasons stated *supra*, the solvates as applied to the above-mentioned compounds claimed by the Applicant are not art-recognized compounds and hence there should be an enabling disclosure in the specification with working example(s).

The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvates of the instant compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance.

The presence or absence of working examples:

There is no working example of any solvate formed. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here.

There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that solvates of these compounds exist and therefore can be made.

The breadth of the claims:

The breadth of the claims include all of the hundreds of compounds of Formula (I) of claim 1 as well as the presently unknown list of potential solvate derivatives embraced by this term. This term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

The specification has no support, as noted *supra*, for the desired solvates of the compounds of Formula (I). As noted above, the genus embraces at least hundreds of compounds and hence the breadth of the claims is broad. The quantity of experimentation needed would be an undue burden on one skilled in the chemical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvates of the compounds of Formula (I) embraced in the instant claims.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claims 33-37, 39, 45-46, 48, -49, 51-52, 54 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual comprising administering a therapeutically-effective amount of a compound of Formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to compositions used to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the

CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual comprising administering a therapeutically-effective amount of a compound of Formula (I).

The state of the prior art:

The state of the prior art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. For example, "the key for the next generation of progress is to unravel the complex effects of activation/antagonism of the various postsynaptic 5-HT receptors and their significance, *if any*, in mediating the antidepressant response." (Emphasis added). Cryan, J., et al., *5-HT_{1A} and Beyond: The Role of Serotonin and its Receptors in Depression and the Antidepressant Response*, Hum. Psychopharmacol. Clin. Exp. 15, 113-135 (2000). This reference shows the speculative nature of the role of 5-HT receptors with the treatment of depression.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to

therapeutic effects, whether or not the compounds of Formula (I) would be useful to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual.

Amount of guidance/working examples:

Although Applicant includes two assays on pages 65-67 of the specification, neither of these definitively show that the instant compounds can reliably be used to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual comprising administering a therapeutically-effective amount of a compound of Formula (I).

The breadth of the claims:

The claim term "a $5HT_{2C}$ receptor associated disorder" is unduly broad because one skilled in the art would not necessarily know what conditions are included by this phrase and which are excluded.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual comprising administering a therapeutically-effective amount of a compound of Formula (I), one

of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to use Applicant's invention to modulate or treat a $5HT_{2C}$ receptor associated disorder, treat disorders of the central nervous system, treat damage to the CNS; treat cardiovascular disorders; treat GI disorders; treat diabetes insipidus or sleep apnea; decrease food intake, control weight gain or induce satiety of an individual comprising administering a therapeutically-effective amount of a compound of Formula (I) without undue experimentation.

Claim Rejections 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

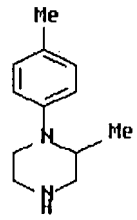
The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 11-12, 17, 19-26, 32 and 79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Allen, et al., U.S. Patent No. 3,751,417.

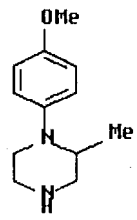
Allen, et al., teaches piperazine compounds useful in the treatment of pain. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious. For example, the following compounds of the reference render instant claim 1 obvious:

2-methyl-1-(4-methylphenyl)-piperazine



when R^2 and R^5 are C_1 alkyl, and R^1, R^3, R^4, R^6 are all H;

1-(4-methoxyphenyl)-2-methyl-piperazine



when R^2 is C_1 alkyl, R^5 is C_1 alkoxy and R^1, R^3, R^4, R^6 are all H;

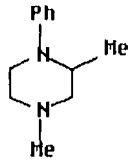
The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Allen, et al.

Claims 1, 3, 11, 12, 17, 19-25 and 79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kametani, et al., *Studies on the Syntheses of Heterocyclic Compounds. CDLX. Benzyne Reaction. XIII. Benzyne Reaction of Halogenobenzenes with N-Alkylmorpholines*, J. Org. Chem., Vol. 37, No. 9, 1450-1453 (1972).

Kametani, et al., teaches piperazine compounds. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious. For example, the following compound of the reference render instant claim 1 obvious:

2,4-dimethyl-1-phenyl-piperazine



when R^1 and R^2 are C_1 alkyl and R^5, R^3, R^4, R^6 are all H;

The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation

of obtaining compounds falling within the generic teaching of claim 1. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Kametani, et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Erich A. Leeser
Patent Examiner, Art Unit 1624
United States Patent and Trademark Office
400 Dulany Street, Remsen 5C11
Alexandria, VA 22314-5774
Tel. No.: (571) 272-9932

James O. Wilson
Supervisory Primary Examiner, Art Unit 1624
United States Patent and Trademark Office
400 Dulany Street, Remsen 5A11
Alexandria, VA 22314-5774
Tel. No.: (571) 272-0661